Citation:

Flood A, Peters U, Jenkins DJ, Chatterjee N, Subar AF, Church TR,Bresalier R, Weissfeld JL, Hayes RB, Schatzkin A; Prostate, Lung, Colorectal, Ovarian (PLCO) Project Team. Carbohydrate, glycemic index, and glycemic load and colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr.* 2006;84(5):1184-92.

PubMed ID: 17093173

Study Design:

Cross-sectional Study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine whether persons with high-glycemic-load diets would be at an increased risk of distal adenomas.

Inclusion Criteria:

- Participants enrolled at 10 cancer screening centers throughout the United States
- Men and women aged 55 - 74 years
- Subjects who had successful sigmoidoscopic exams (insertion to 50 cm with >90% mucosa visible or suspect lesion found)

Exclusion Criteria:

- Self-reported history of cancer other than basal-cell skin cancer.
- Self-reported history of ulcerative colitis, Crohn disease, familial polyposis, colorectal polyps, or Gardner syndrome.
- Extreme values (ie, lowest and highest 1%) on sex-specific energy intake and missing >7 items in the food-frequency questionnaire.
- Some participants will be excluded for more than one reason.

Description of Study Protocol:

Recruitment

- Between September 1993 and September 2000, 77,470 men and women aged 55–74 y were randomly assigned to the screening arm of the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Trial.
- The PLCOstudy randomly assigned subjects at entry into either a screening arm (where the subjects would undergo screening for each of these 4 cancer sites) or into a usual care arm.
- Participants enrolled at 10 screening centers throughout the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC).

Design: Cross-Sectional Study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- The prevalence odds ratios (OR) and 95% CIs for sigmoidoscopy-detected, distal adenomas using logistic regression analysis (SAS version 8.2; SAS Institute Inc, Cary, NC) for energy-adjusted quintiles of dietary carbohydrate, glycemic index, and glycemic load based on the distribution in controls was conducted.
- To test for confounding, models that entered each of these variables one at a time and then models that entered all simultaneously was used. Residual method was used to adjust glycemic load, glycemic index, and carbohydrate for energy intake.
- Stratified analyses are conducted to explore effect modification for selected factors including BMI, history of diabetes, and physical activity. The *P* value for trend was estimated by using carbohydrate, glycemic index, and glycemic load as continuous variables. All *P* values were two-sided.

Data Collection Summary:

Timing of Measurements

One time measurements completed at screening. At the time of initial screening, the participants filled out a risk factor questionnaire about sociodemographic factors, smoking history, use of selected drugs, disease history, family history of cancer, recent history of screening examinations, height, weight, and physical activity.

Dependent Variables

- Risk of colorectal adenomas
- The participants whose sigmoidoscopic exam was suspicious for neoplasia (ie, a polyp or mass) were referred to their primary care physician for further care and possible endoscopic follow-up. Medical-pathologic reports on the removed lesions were obtained and coded by trained medical abstractors.

Independent Variables

- Carbohydrate, glycemic index and glycemic load
- 137-item FFQ to assess usual dietary intake for each participant over the 12 mo before enrollment. The FFQ provided information for the ascertainment of portion size for all food items except for fruit and vegetables.

Control Variables

- Family history of colorectal cancer
- Ethnicity (white or nonwhite)
- Physical activity
- Regular use of aspirin or ibuprofen in the preceding 12 mo
- Smoking
- Education
- Alcohol consumption
- Energy-adjusted dietary calcium and calcium from supplements
- Energy-adjusted average daily red meat consumption

- Total folate intake

Description of Actual Data Sample:

Initial N: 77,470 men and women originally randomized to the screening arm. Successful sigmoidoscopic exams were carried out for 57,569 participants, among whom 52,143 (90.6%) also provided risk factor and dietary information.

Attrition (final N): After application of exclusion criteria, data for 44,572 participants were available for analysis (24,017 men and 20,555 women).

Age: aged 55 - 74 years

Ethnicity: not described

Other relevant demographics:

Anthropometrics

Location:

Participants enrolled at 10 screening centers throughout the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC).

Summary of Results:

Odds ratios (ORs) and 95% CIs for distal colorectal adenoma in men by quintile (Q) of energy-adjusted available carbohydrate, glycemic index, and glycemic load*1*

	All adenomas (2378 cases)			Advanced adenomas (929 cases)		
	Minimally adjusted*2*	Fully adjusted*3*	Additionally adjusted for fiber*4*	Minimally adjusted*2*	Fully adjusted*3*	Additionally adjusted for fiber*4*
Glycemic index*5* Q1 (<52.1)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2 (52.1–54.0)	0.91 (0.79, 1.04)	0.94 (0.82, 1.09)	0.94 (0.81, 1.09)	0.82 (0.66, 1.03)	0.87 (0.69, 1.09)	0.86 (0.69, 1.08)
Q3 (54.1–55.7)	1.04 (0.91, 1.19)	1.08 (0.93, 1.24)	1.06 (0.91, 1.22)	1.03 (0.83, 1.26)	1.07 (0.86, 1.33)	1.05 (0.84, 1.31)
Q4 (55.8–58.0)	1.11 (0.97, 1.27)	1.13 (0.98, 1.31)	1.10 (0.94, 1.27)	1.06 (0.86, 1.30)	1.09 (0.87, 1.37)	1.05 (0.84, 1.32)
Q5 (> 58.0)	1.08 (0.95, 1.24)	1.05 (0.90, 1.23)	0.98 (0.84, 1.15)	1.06 (0.86, 1.30)	1.03 (0.81, 1.31)	0.95 (0.75, 1.22)
P for trend	0.06	0.25	0.87	0.07	0.13	0.47
Glycemic load*5* Q1 (< 122)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2 (122–138)	0.87 (0.77, 0.99)	0.99 (0.87, 1.12)	1.02 (0.89, 1.16)	0.87 (0.72, 1.05)	0.98 (0.81, 1.20)	1.02 (0.83, 1.24)
Q3 (139–151)	0.72 (0.63, 0.82)	0.87 (0.76, 1.00)	0.91 (0.79, 1.05)	0.61 (0.50, 0.75)	0.75 (0.61, 0.94)	0.80 (0.64, 1.00)
Q4 (152–166)	0.66 (0.58, 0.75)	0.83 (0.72, 0.96)	0.88 (0.75, 1.02)	0.63 (0.51, 0.77)	0.80 (0.64, 1.00)	0.85 (0.68, 1.07)
Q5 (>166)	0.60 (0.52, 0.69)	0.79 (0.68, 0.93)	0.84 (0.71, 0.98)	0.59 (0.48, 0.73)	0.79 (0.62, 1.00)	0.84 (0.66, 1.08)
P for trend	<0.0001	<0.003	<0.03	<0.0001	0.11	0.37

1 n = 20 172 men. ORs and 95% CIs were calculated by using logistic regression.
*2*Controlled for age at randomization, energy, BMI, and study center.
3 Adjusted for age at randomization, energy, BMI, study center, family history of colorectal cancer, ethnicity, physical activity, aspirin and ibuprofen use,
smoking, education, alcohol use, dietary calcium and calcium from supplements, red meat consumption, and total folate intake.
4 Adjusted for all covariates in the fully-adjusted model plus fiber.
5 Energy-adjusted by using residual method.

Key Findings

- For glycemic index, there was no significant interaction, but for clarity and consistency of presentation, we also provided these results stratified by sex. In the analyses of all adenomas (both advanced and nonadvanced), the ORs were dramatically reduced with increasing intakes of carbohydrate for both men and women in unadjusted models, although the association was somewhat less pronounced in the women (OR for quintile 5 compared with quintile 1 for the men: 0.52; 95%CI: 0.45, 0.60;P for trend<0.0001;OR for the women: 0.74; 95% CI: 0.62, 0.89; P for trend<0.0005).
- These associations were attenuated in multivariate-adjusted models such that they remained highly statistically significant in men (OR: 0.71; 95% CI: 0.60, 0.84; P for trend<0.0001), but in women they did not (OR: 0.89; 95% CI: 0.73, 1.10; P for trend<0.30). Of the variables in the fully adjusted model, smoking accounted for the greatest portion of the attenuation in men and women, and 4 variables together (smoking, alcohol, folate, and red meat) accounted for essentially all of the attenuation.
- The estimated ORs for glycemic load and adenomas closely mirrored those of carbohydrate (OR for quintile 5 compared with quintile 1 in multivariate-adjusted models for men: 0.79;95%CI: 0.68, 0.93; P for trend <0.003; and OR for women: 0.98; 95% CI 0.81, 1.19; P for trend <0.70).

Other Findings

- In both sexes, those with a higher glycemic load tended to be slightly older, more frequently of nonwhite ethnicity, more physically active, of somewhat lower BMI, and much less likely to have a history of smoking. Persons in the high-glycemic-load quintile, although not differing significantly from those in the low quintile in vegetable consumption, did consume much more fruit, more grains (especially whole grains), slightly more calcium (including supplements), less red meat, and less alcohol.
- The percentage of calories from fat decreased sharply as glycemic load increased. Fat and total carbohydrate are inversely correlated in this cohort (r=0.46 for women and 0.28 for men; P< 0.0001 for both) and that total carbohydrate is in part what determines glycemic load.
- Carbohydrate,however, was much more strongly correlated with glycemic load than was glycemic index (r=0.92 in men and 0.89 in women for carbohydrate, and r =0.48 in men and 0.42 in women for glycemic index).
- Total dietary fiber was strongly correlated with carbohydrate in this cohort (r = 0.54 in men and 0.47 in women), the glycemic index showed only minimal correlation with carbohydrate (r = 0.11 in men and 0.04 in women).
- The correlation between fiber and glycemic index was only -0.24 in men and -0.34 in women.
- Models with interaction terms for sex indicated significant effect modification (P<0.001) for both available carbohydrate and glycemic load.
- Tests of interaction, however, showed no significant effect modification by BMI above or below the 25 kg/m$_2$ threshold. As with BMI, tests of interaction provided no evidence of a significant effect modification by level of physical activity.

Author Conclusion:

There was no significant increased risk with higher glycemic load, carbohydrate intake, or glycemic index, and, in fact, the data showed a reduction in risk for distal adenomas among men with higher carbohydrate intake (and glycemic load). Control for fiber resulted in no significant change in these associations. Given the divergence of these results from previous reports linking glycemic load to indicators of insulin resistance and related factors to colorectal outcomes, and given the sparse and inconsistent evidence available from studies directly connecting glycemic load and colorectal neoplasia, there is a clear need for additional research in this area.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes